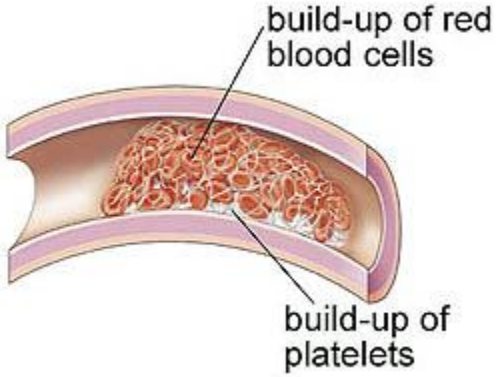

Thrombophilia – Hypercoagulable States

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Objective

By the end of this lecture the student must be able to:

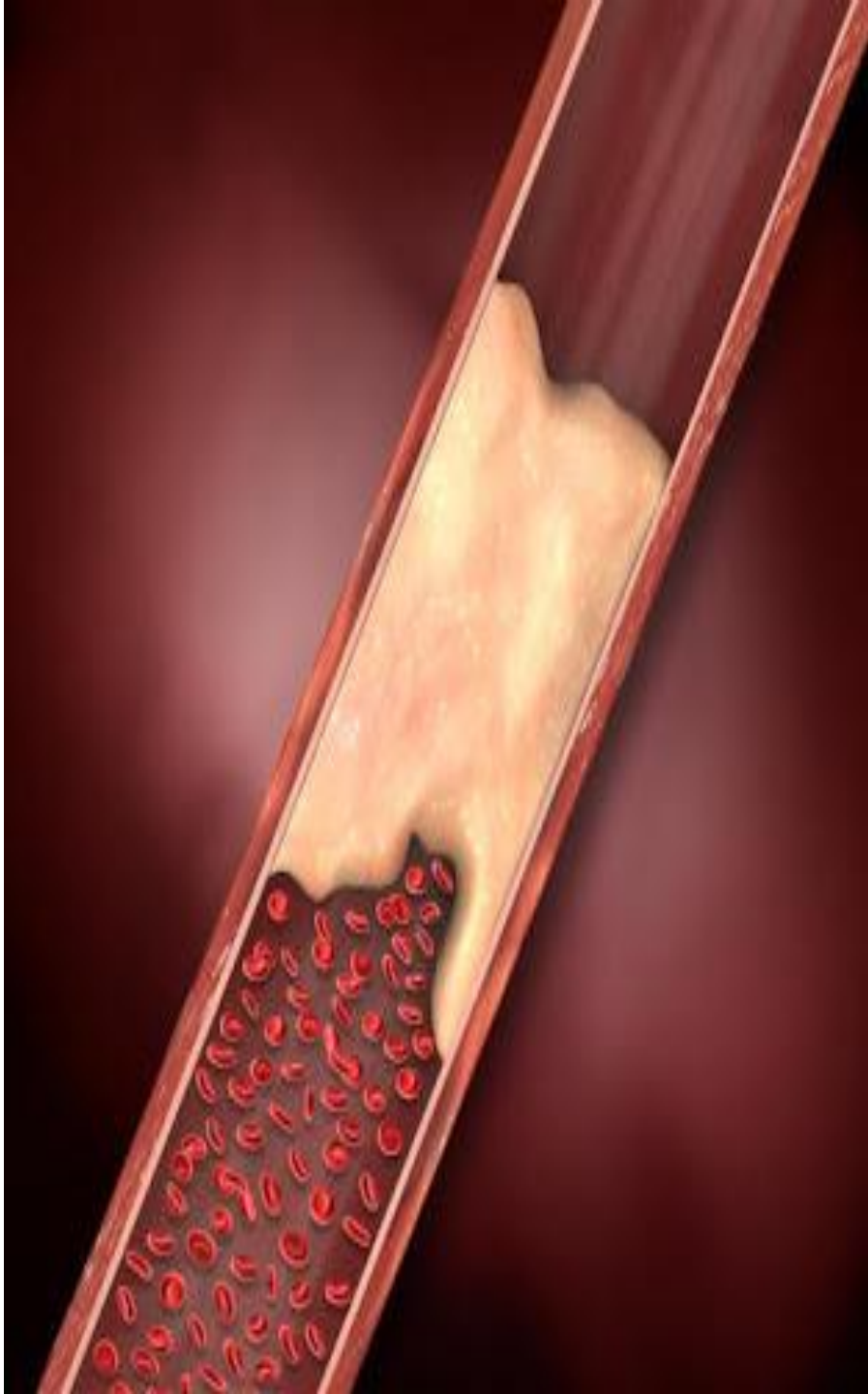
- Define hypercoagulablility “thrombophilia”.
- Enumerate the causes of hypercoagulability.
- Clinical evaluation of thrombophilic patients.
- Enumerate screening tests needed to diagnose a thrombophilic case.
- Enumrate laboratory tests needed to diagnose a thromboembolic case.

Hypercoagulability;

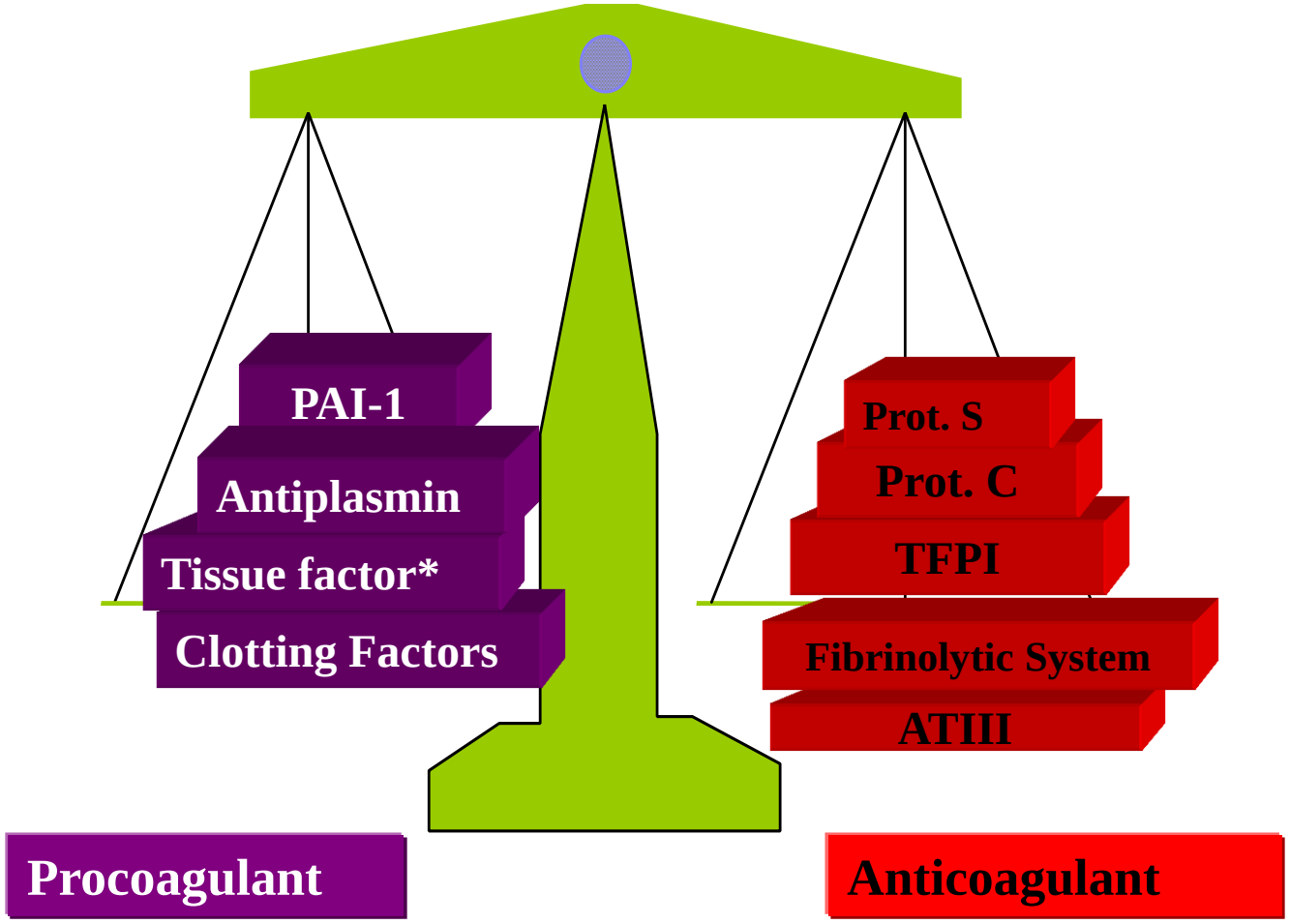
“Thrombophilia”:

Predisposition
for thrombotic events,
(arterial or venous).

- Deep vein thrombosis
- Pulmonary embolism



Hemostatic Balance



Fibrinolytic system: restriction of clotting to local site of injury

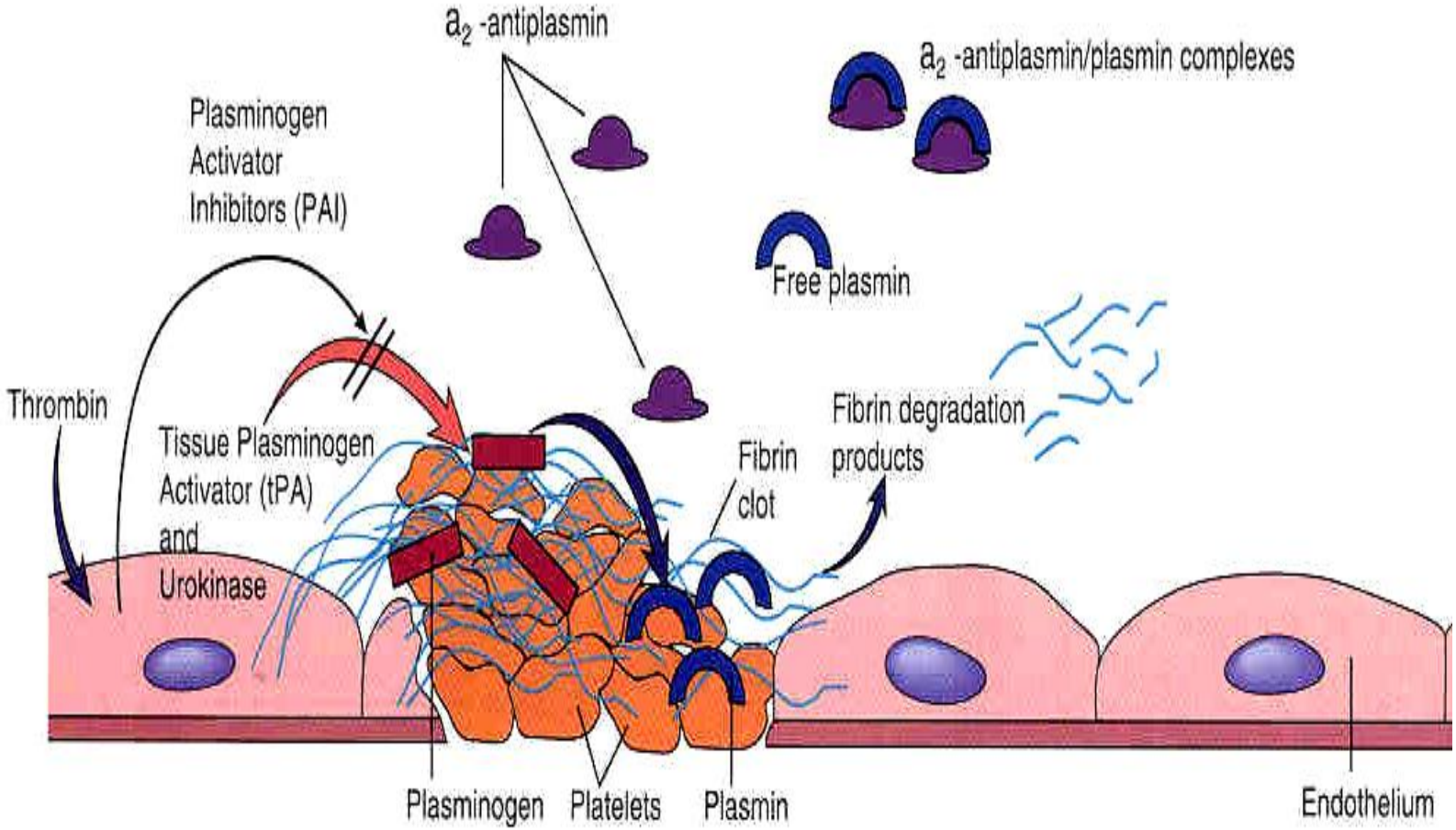
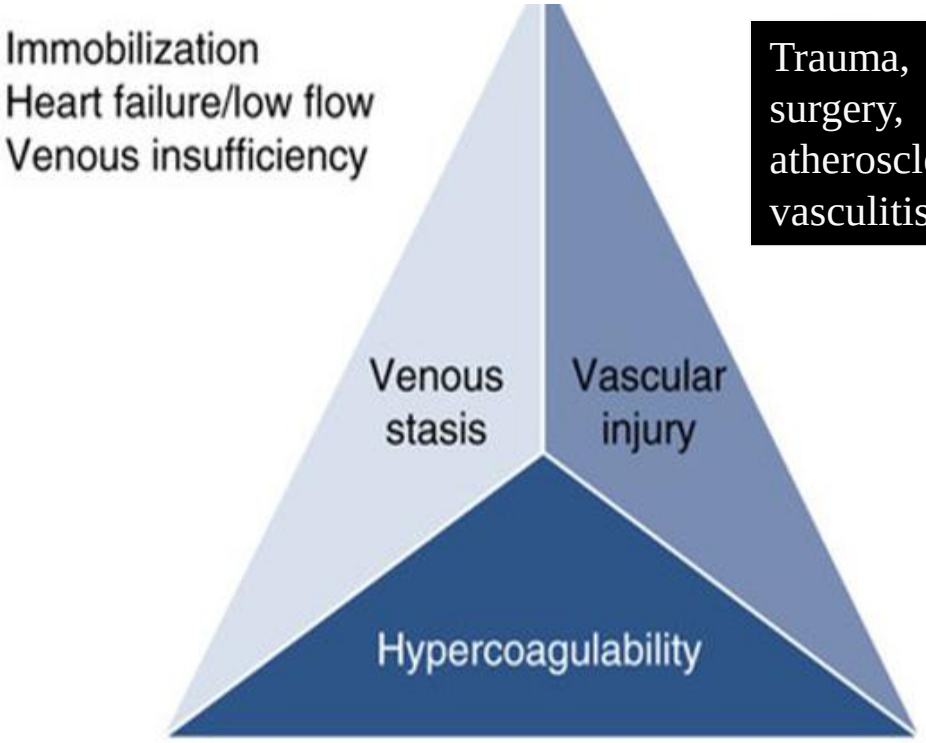


Fig. 4-12, Pathologic Basis of Disease, 2005

Virchow's triad in thrombosis

- **Endothelial injury**
- **Venous Stasis** or abnormal blood flow
- **Hypercoagulability**:
- ↓ levels of inhibitor of coagulation protein C & S.
- ↑ promoter of coagulation (fibrinogen, factors VII and VIII & VWF .
- Reduced fibrinolysis (due to ↑ synthesis of plasminogen activator inhibitors).



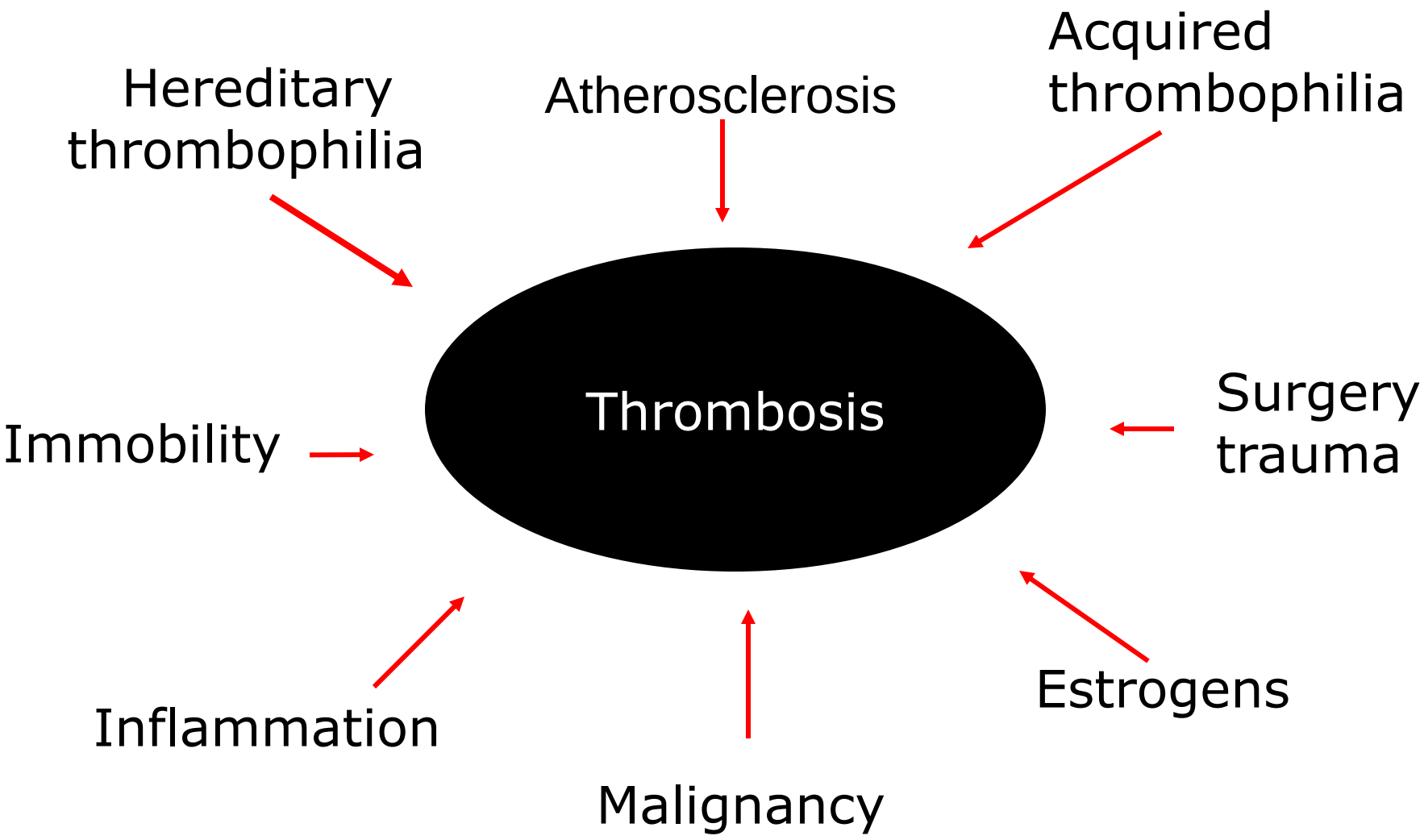
Thrombosis

Arterial thrombosis

- Mainly related to **endothelial injury risk factors.**
- E.g., atherosclerosis of the vessel wall with risk factors such as hypertension, smoking, hyperlipidaemia, & diabetes.

Venous thrombosis

- Mainly related to both **hypercoagulability & stasis risk factors.**
- E.g., genetic coagulation factor abnormalities (factor V leiden), stasis of the circulation or to an acquired increase in coagulation factors (e.g Oestrogen therapy, postoperative, pregnancy) or to unknown factors (e.g age or obesity)


Hereditary thrombophilia
Atherosclerosis
Acquired thrombophilia
Thrombosis
Immobility
Surgery trauma
Inflammation
Malignancy
Estrogens

Risk Factors for Thrombophilia

Types of inherited

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin gene mutation
- Dysfibrinogenaemia
- Plasminogen deficiency
- Hyperhomocysteinaemia
- Sickle cell disease.

Causes of acquired

- Aging
- Nephrotic syndrome
- Malignancy
- Dehydrosis, Hyperviscosity
- Blood disorders (polycythaemia, MPD, PNH)
- DIC
- Pregnancy/ postpartum
- Oestrogen therapy,(OCP)
- Inflammation(Behcet's disease, SLE)
- Antiphospholipid antibody syndrome (lupus anticoagulants)
- Long flight (>4 hours)
- Varicose vein
- Heparin-induced thrombocytopenia (HIT)
- Immobilization, Post operative
- Smoking, Obesity

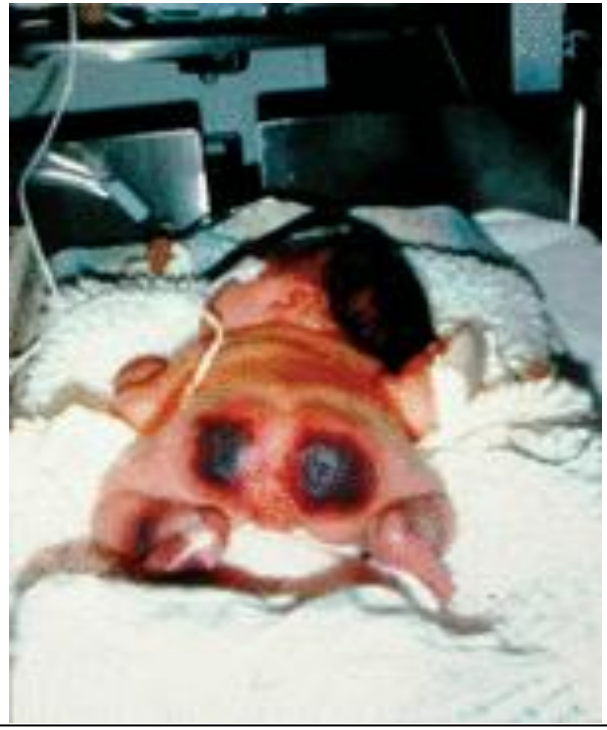
Antithrombin Deficiency

- ATIII inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (IIa), IXa, Xa, XIa and XIIa.

- Antithrombin's deficiency is an AD.
- Recurrent venous thrombosis usually start early in life.
- Arterial thrombosis occur occasionally.

Protein C and Protein S Deficiency

- Protein C & Protein S are vitamin K dependent glycoproteins produced in the liver
- Activated protein C (APC) bind with protein S to degrade factors Va and VIIIa, limiting thrombin production
- Protein C deficiency, whether inherited (AD) or acquired, may cause thrombosis when levels drop to 50% or below
- Acquired protein C deficiency also occurs with surgery, trauma, pregnancy, OCP, liver or renal failure, DIC, or warfarin



"neonatal purpura fulminans", homozygous deficiencies of protein C or S.

Activated Protein C (APC) Resistance Due to Factor V Leiden

- Factor V Leiden is an alterations of the factor V molecule at APC binding sites A506G (substitution of Arginine at position 506 amino acid by glutamine), which impair, or resist APC's ability to degrade or inactivate factor Va .

Prothrombin G20210A Mutation

- A G-to-A substitution in nucleotide position 20210 is responsible for a factor II polymorphism.

- This mutation causes a 30% increase in prothrombin levels and increase thrombotic risk by 5 folds.

Antiphospholipid Syndrome (APS)—Diagnosis

It is a syndrome with 2 criteria:

- **Clinical Criteria**

  - Arterial or venous thrombosis.

  - (+/-) Recurrent miscarriage.

  - Laboratory evidence of persistent antiphospholipid antibody (β2-GPI-1) .

- **Laboratory Criteria**

  - Persistent to IgG or IgM anticardiolipin antibody which is antiphospholipid antibody, (β2- glycoprotein)

  -Lupus Anticoagulant (LAC is one of APS. Identified by prolonged plasma APTT which doesn’t correct with 1:1 mixing test).

The most prevalent Thrombophilic Defects;

- Antithrombin deficiency,
- Protein C deficiency,
- Protein S deficiency,
- Lupus Anticoagulant.

Site of Thrombosis
" arterial vs venous"

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin G20210A	-	+
Antithrombin deficiency	-	+
Protein C deficiency	-	+
Protein S deficiency	-	+
Hyperhomocysteinemia	+	+
Lupus Anticoagulant	+	+

How Do You Decide Who to Test?

Patients may be candidates for screening for hypercoagulable states if they have:

- Positive **family** history
- Age of **onset <50**
- **Thrombosis in unusual locations or sites**, such as veins in the arms, liver (portal), intestines (mesenteric), kidney (renal) or brain (cerebral)
- Blood clots that occur without a clear cause (**idiopathic**)
- A history of **recurrent** thrombosis
- A history of **frequent miscarriages**

Evaluation For Thrombophilic Patients

- History & examination:
- Onset of episode.
- Family history.
- Past medical history of underlying condition associated with VTE.
- Risk factors for VTE
- Medication predispose to VTE.

Screening Tests For "Thrombophilic" Patients

- CBC (HCT, platelet count).
- ESR
- Blood smear (? Blood disorder)
- APTT & PT (shorten time except in LAC)
- TT (abnormal fibrinogen)
- Fibrinogen level
- Factor VIII level.
- JAK2 mutation for Polycythaemia Rubra Vera (PRV).
- Flow cytometry for PNH (CD59 , CD 55)
- Protein electrophoresis for paraprotein.

Screening Tests For "Thrombophilic" Patients

- Test for Factor V Leiden
- Genetic test for prothrombin gene mutation 20210A
- Functional assay of antithrombin
- Functional assay of protein C
- Functional assay of protein S
- Clotting test for lupus anticoagulant/ELISA for cardiolipin antibodies
- Measurement of fasting total plasma homocysteine

Diagnosis of a patient with venous thrombosis

- Clinical suspicion: DVT is suspcted in those with previous DVT, cancer, or bed ridden. In the leg unilateral thigh or calf swelling or tenderness, pitting edema & or presence of collateral superficial non varicose veins . Homan”n sign(pain in the calf on flexing the ankle).b
- Plasma D-dimer conc.
- Serial compression ultrasound
- Contrast venography
- MRI

Diagnosis of a patient with Pulmonay embolus

- **Clinical suspicion**: this is suspected in patient with chest symptom especially if there are signs or previous history of DVT, immobilization for > 2 days, recent surgery <4 weeks, hemoptysis or cancer.

- **Pulmonary embolus is diagnosed by** :
- Chest X ray, Pulmonary CT, MRI Pulmonary angiography, Pulmonary angiography, Electrocardiogram.
- D- dimer (marker of fibrinlysis)
- Thromboelastometry .

WELLS SCORE

(**Wells score,** is a useful assay when DVT is suspected).

Table Wells Model for DVT Assessment

Clinical Parameter Score	Score
Active cancer (treatment ongoing, or within 6 months or palliative)	+1
Paralysis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for >3 days or major surgery <4 weeks	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling >3 cm compared with the asymptomatic leg	+1
Pitting edema (greater in the symptomatic leg)	+1
Previous DVT documented	+1
Collateral superficial veins (non-varicose)	+1
Alternative diagnosis (as likely or greater than that of DVT)	-2
Total Score	

High probability	>3
Moderate probability	1 or 2
Low probability	<0

Source: Adapted from: Wells PS, et al. *JAMA* 2006;295:199–207.

Predictors for Recurrent VTE

- Idiopathic VTE
- Residual DVT
- Elevated D-dimer levels
- Age
- Sex

Specific tests for excluding the underlying acquired causes;

- HIT test, Heparin antibody (IgG detection by ELISA)
- Imaging to screen for malignancy (Xray, abd CT, abd U/S).
- Tumor marker (PSA, CA 125,..) for occult malignancy.
- Exclude nephrotic (24 hour urine collection for protein)
- Serum albumin, creatinine, triglycerides & cholesterol ..

Anticoagulant drugs

- Heparin can be given in the unfractionated form. Much more frequently low molecular weight heparin is given SC.
- Warfarin is the frequently used oral anticoagulant, the dose usually aimed to raise the international normalization ratio (INR) between 2 and 3.
- Thrombi if fresh may be dissolved by fibrinolytic agents (streptokinase) or r-TPA.
- Antiplatelet drugs-Aspirin, Clopidogrel, and Dipyridamol are used to treat arterial disclosure

Text book

- Chapters 27 , Essential Haematology by AV Hoffbrand, JE Pettit and PAH Moss, 6th Edition 2011, Blackwell Science